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INTERNATIONAL PRELIMINARY EXAMINING AUTHORITYBARKER BRETTELL
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To:

PEEL, James P.
BARKER BRETTELL
10-12 Priests Bridge
London SW15 5JE
GRANDE BRETAGNE

RECORDS DEPT.

SEEN BY: TO

AGENT: JPP

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing
(day.month.year)

15.07.2004

Applicant's or agent's file reference
JPP183

IMPORTANT NOTIFICATION

International application No.
PCT/GB 03/00966International filing date (day.month.year)
07.03.2003Priority date (day.month.year)
07.03.2002Applicant
ROYAL HOLLOWAY UNIVERSITY OF LONDON, et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international
preliminary examining authority:European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Brandt, M

Tel. +49 89 2399-2926



PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT (PCT Article 36 and Rule 70)

Applicant's or agent's file reference JPP183	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)
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International application No. PCT/GB 03/00966	International filing date (day/month/year) 07.03.2003	Priority date (day/month/year) 07.03.2002
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International Patent Classification (IPC) or both national classification and IPC
C12N3/00



Applicant
ROYAL HOLLOWAY UNIVERSITY OF LONDON, et al.

- This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
- This REPORT consists of a total of 6 sheets, including this cover sheet.
☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 507 of the Administrative Instructions under the PCT).

These annexes consist of a total of 5 sheets.

- This report contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 02.10.2003	Date of completion of this report 15.07.2004
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Rojo Romeo, E Telephone No. +49 89 2399-7321 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB 03/00966

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-37 as originally filed

Claims, Numbers

1-30 received on 25.02.2004 with letter of 20.02.2004

Drawings, Sheets

1/14-14/14 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/GB 03/00966**

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	10, 12-17, 20, 21
	No: Claims	1-9, 11, 18, 19, 22-30
Inventive step (IS)	Yes: Claims	
	No: Claims	1-30
Industrial applicability (IA)	Yes: Claims	1-30 (see comment for claims 29 and 30)
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents cited in the International Search Report:

D1: WO 02 00232 A (MAXYGEN INC ;GOLDMAN STANLEY (US); WHALEN ROBERT G (US); LATHROP S) 3 January 2002 (2002-01-03)

1. Novelty (Art. 33(2) PCT)

D1 discloses recombinant spores expressing peptides. These spores are useful as therapeutic or prophylactic agents or vaccines against a broad spectrum of immunogens and bacterial and viral pathogens. The spores used can be viable or not (see page 11). The ways of delivery of the recombinant spores are respiratory, nasal, parenteral, and mucosal. It is contemplated to use one or several plasmids, thus giving the possibility to express several peptides (see pages 4-5, example 11). Fig. 4 discloses the spore surface display of a Yersinia pestis V antigen fused to the CotC spore coat protein of B. subtilis and a viral epitope exemplified by HA1. Fig. 12 is concerned with a fusion to CotV and Fig. 9-11 disclose the oral administration of the recombinant spores to mice to test for efficacy. Various fusions to spore coat proteins are contemplated (see page 22: CotC, CotG, CotD, etc.)

Claim 1 is now drawn as a first medical use. This is a product claim. For the purpose of the international examination, the terms for "use in" are to be read as "suitable for". The spores described in D1 (see e.g. example 9) are Bacillus spores displaying the Yersinia V antigen on the surface as a fusion protein with CotC. These spores were used for and are thus suitable for oral administration. Thus, D1 is novelty destroying for the subject-matter of claims 1-9, 11, 18, 19, 22-30.

In addition, Applicant's attention is drawn to the fact that these spores were also used for nasal administration and shown to provide a therapeutic effect using this way of administration (see Fig. 10: titer of around 10000 with V7 recombinant spores alone). A therapeutic use of "a Bacillus spore which is genetically modified with genetic code comprising at least one genetic construct encoding a therapeutic active compound and a targeting sequence or a vegetative cell protein" was therefore already known from prior art. A first medical use claim is thus not suitable.

When used orally, the recombinant spores disclosed in D1 do not lead to a significant

titre. The present set of claims does not contain any additional technical feature when compared to the disclosure of D1. No such technical feature is clearly recognisable in the description. An additional objection for lack of disclosure therefore arises (Art. 5 PCT).

D1 is thus novelty destroying for the subject-matter of claims 1-9, 11, 18, 19, 22-30.

2. Inventive step (Art. 33(3) PCT)

2.1 D1 already discloses the use of various antigens amongst which tetanus is found (page 62). The choice of a fragment of tetanus toxin fragment C or labile toxin B subunit is just an alternative choice of an antigen and does not show any inventive activity. Thus, claim 10 is not inventive. The same applies to the subject-matter of claims 12, 20 and 21.

2.2 In the absence of a surprising effect/advantage due to the choice of the specific proteins rmO or oppA to construct the claimed fusion proteins when compared to already disclosed recombinant spores expressing similar fusion proteins with the same aims of providing e.g. vaccines and therapeutic compounds, the subject-matter of claims 13-17 does not show any inventive activity.

Consequently, claims 1-30 lack inventive step.

3. Industrial applicability (Art. 33(4) PCT)

For the assessment of the present claims 29 and 30 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

4. Additional remarks

Applicant's attention is drawn to the fact that the present set of claims is very unclear and not representative of the subject-matter disclosed in the application as filed. Additional objections for lack of clarity, support by the specification and complete

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB03/00966

disclosure of the invention are to be expected in the regional phase.

CLAIMS

1. A Bacillus spore which is genetically modified with genetic code comprising at least one genetic construct encoding a therapeutically active compound and a targeting sequence or a vegetative cell protein for use in oral administration for therapeutic treatment.
2. A spore as claimed in Claim 1 characterised in that the therapeutically active compound is an antigen or a medicament or a precursor to an antigen or a medicament.
3. A spore as claimed in Claim 1 or Claim 2 characterised in that the gene construct is a chimeric gene.
4. A spore as claimed in any one of the preceding Claims characterised in that the genetic modification is accomplished by transformation of a mother cell using a vector containing the gene construct and then inducing the mother cell to produce spores as defined in any one of the preceding Claims.
5. A spore as claimed in any one of the preceding Claims characterised in that the gene construct is under the control of one or more of, each or independently, an inducible promoter, a promoter or a strong promoter or modified promoter.
6. A spore as claimed in Claim 5 characterised in that the gene construct has an enhancer element or an upstream activator sequence associated with it.

7. A spore as claimed in any one of the preceding Claims characterised in that the construct comprises an inducible expression system.
- 5 8. A spore as claimed in any one of the preceding Claims characterised in that the spore germinates in the duodenum and/or the jejunum of an intestinal tract of a human or animal body.
9. A spore as claimed in any one of the preceding Claims
10 characterised in that the therapeutically active compound is an antigen which, in use, is adapted to elicit an immune response.
10. A spore as claimed in Claim 9 characterised in that the antigen is at least a fragment of tetanus toxin fragment C or labile toxin B sub unit.
- 15 11. A spore as claimed in any one of the preceding Claims characterised in that the protein is a protein that is expressed in the cell barrier.
- 20 12. A spore as claimed in any one of the preceding Claims characterised in that the protein is expressed all the time in a vegetative cell.
13. A spore as claimed in Claim 12 characterised in that the protein is
25 OppA or rrnO.
14. A spore as claimed in any one of Claims 1 to 11 characterised in that the protein is expressed intermittently in a vegetative cell.
- 30 15. A spore as claimed in any one of Claims 1 to 10 characterised in that the protein is a soluble cytoplasmic vegetative cell protein.

16. A spore as claimed in Claim 15 characterised in that the protein is rrnO.

5 17. A spore as claimed in Claim 15 or Claim 16 characterised in that the genetic construct of the soluble cytoplasmic protein wholly or partially comprises a signal sequence.

10 18. A spore as claimed in any one of Claims 1 to 10 characterised in that the signal sequence is adapted to target the therapeutically active compound to a specific part of the vegetative cell.

15 19. A spore as claimed in Claim 18 characterised in that the signal sequence directs the therapeutically active compound for secretion (preferably active secretion, more preferably Type I, Type II or Type III secretion), or for post-translational processing by a vegetative cell (preferably glycosylation).

20 20. A spore as claimed in any one of the preceding Claims characterised in that the therapeutically active compound is an antigen precursor which is one or more enzymes capable of transforming a biological precursors, such that upon germination said one or more enzymes are expressed and synthesise one or more antigens by transformation of a said biological precursor.

25

21. A spore as claimed in Claim 20 characterised in that the biological precursor is a hormone, a steroid hormone, a painkiller or a pro-drug.

30 22. A spore as claimed in any one of Claims 1 to 19 wherein the therapeutically active compound is a medicament which is a protein, a vaccine or an endorphin.

23. A spore as defined in any one of the preceding Claims characterised in that it is for use in treatment of a medical condition, preferably the medical condition is inflammation, pain, a hormonal
5 imbalance and/or an intestinal disorder.

24. A composition comprising at least two different spores as defined in any one of the preceding Claims characterised in that said at least two different spores express at least two different therapeutically active
10 compounds.

25. A composition as defined in Claim 24 characterised in that the composition further comprises a pharmaceutically acceptable excipient or carrier.
15

26. A composition comprising a spore as defined in any one of claims 1 to 23 in association with a pharmaceutically acceptable excipient or carrier.

20 27. A composition as defined in any one of Claims 24 to 26 for use in treatment of a medical condition, preferably the medical condition is inflammation, pain, a hormonal imbalance and/or an intestinal disorder.

28. Use of a spore as defined in any one of claims 1 to 23 in the
25 manufacture of a medicament for use in the treatment of a medical condition, preferably the medical condition is inflammation, pain, a hormonal imbalance and/or an intestinal disorder.

29. A method of medical treatment, which method comprises the steps
30 of

- 5

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INTERNATIONAL SEARCH REPORT

Intern: Application No
PCT, 03/00966

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N3/00 C12N15/00 A61K39/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N A61K

~~Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched~~

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, WPI Data, PAJ, MEDLINE, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02 00232 A (MAXYGEN INC ;GOLDMAN STANLEY (US); WHALEN ROBERT G (US); LATHROP S) 3 January 2002 (2002-01-03)	1-8, 10-12, 17,18, 23-31
Y	in particular, examples and claims. the whole document	11
X	WO 01 94599 A (KATAGIHALLIMATH NAINESH ;MUKHERJEE KAKOLI (IN); SMITTSKYDDSinSTITU) 13 December 2001 (2001-12-13)	1-13, 15-20, 23-31
Y	the whole document	11

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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

^a Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *S document member of the same patent family

Date of the actual completion of the international search

26 May 2003

Date of mailing of the international search report

10/06/2003

Name and mailing address of the ISA
European Patent Office, P.O. 5618 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 eps nl,
Fax: (+31-70) 340-3016

Authorized officer

Rajo Romeo, E

INTERNATIONAL SEARCH REPORT

Intern: Application No
PCT, 00 03/00966

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ROBINSON K ET AL: "ORAL VACCINATION OF MICE AGAINST TETANUS WITH RECOMBINANT LACTOCOCCUS LACTIS" NATURE BIOTECHNOLOGY, NATURE PUBLISHING, US, vol. 15, no. 7, 15 July 1997 (1997-07-15), pages 653-657, XP001093957 ISSN: 1087-0156 the whole document	11
X	MINTON NIGEL P ET AL: "Chemotherapeutic tumour targeting using clostridial spores." FEMS MICROBIOLOGY REVIEWS, vol. 17, no. 3, 1995, pages 357-364, XP002242524 ISSN: 0168-6445 the whole document	21,22

INTERNATIONAL SEARCH REPORT

Internal application No
PCT/GB U3/00966

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0200232	A	03-01-2002	AU 7300901 A	08-01-2002
			EP 1299115 A2	09-04-2003
			WO 0200232 A2	03-01-2002
			US 2002150594 A1	17-10-2002
WO 0194599	A	13-12-2001	AU 6448801 A	17-12-2001
			EP 1292686 A1	19-03-2003
			WO 0194599 A1	13-12-2001